IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
REQUEST FOR FILING APPLICATION UNDER RULE 53(b)

Pursuant to 37 CFR 1.53(b), please file a ☐ continuation/☒ divisional of the pending prior PATENT APPLICATION of:
Inventor: FERGUSON, Mark W.J.
Serial No. 09/029,098
Filed: May 13, 1998
For: **PHARMACEUTICAL COMPOSITION CONTAINING INHIBITORS OF INTERFERON-GAMMA**

Atty Dkt.: 39-196
C# M#
Date: December 14, 1999
Group: 1646
Examiner: Fitzgerald, D.

jc639 U.S. PTO 12/14/99

jc675 U.S. PTO 09/459979 12/14/99

Assistant Commissioner for Patents
Washington, DC 20231
Sir:

This request for filing under Rule 53(b) is made by the following named inventor(s) (using the above-identified title):
Inventor(s): FERGUSON, Mark W.J.

☒ Attached is a true copy of the prior application as originally filed including the specification, claims, Oath/Declaration and drawings (if any) and abstract (if any). No amendments (if any) referenced in the Oath or Declaration filed to complete the prior application introduced new matter.

☒ Priority is hereby claimed under 35 USC 119 based on the following foreign applications, the entire content of which is hereby incorporated by reference in this application:

Application Number	Country	Day/Month/Year/Filed
9516967.8	Great Britain	18 August 1995

☐ certified copy(ies) of foreign application(s) attached or
☐ already filed on _____ in prior appln. no. _____ filed _____
☒ already filed in PCT/GB96/01949 filed 09 August 1996

☐ Please amend the specification by inserting before the first line: -- This application claims the benefit of U.S. Provisional Application No. , filed , the entire content of which is hereby incorporated by reference in this application.--

☒ The prior application is assigned to THE VICTORIA UNIVERSITY OF MANCHESTER.

☒ Power of Attorney has been granted to Mary J. Wilson et al, Reg. No. 32,955 of Nixon & Vanderhye P.C., 1100 N. Glebe Rd., 8th Flr, Arlington, VA 22201.

☒ Address all future communications to: Nixon & Vanderhye P.C., 1100 N. Glebe Rd., 8th Floor, Arlington, VA 22201.

☒ Please amend the specification by inserting before the first line --This is a divisional of application Serial No. 09/029,098, filed May 13, 1998, now pending, which is a 371 of PCT/GB96/01949, filed August 9, 1996 , the entire content of which is hereby incorporated by reference in this application.--

☒ "Small entity" statement of record. ☐ "Small entity" statement attached.

☐ Petition filed in prior application to extend its life to insure copendency.

☒ The Examiner's attention is directed to the prior art cited in the parent application by applicant and/or Examiner for the reasons stated therein.

☒ Please enter the attached and/or below preliminary amendment **prior** to calculation of filing fee:

☒ The entire disclosure of the prior application above-referenced is considered as being part of the disclosure of this new application and is hereby incorporated by reference therein.

FILING FEE IS BASED ON CLAIMS AS FILED LESS ANY HEREWITH CANCELED

Basic Filing Fee						$	760.00
Total effective claims	8	- 20 (at least 20) =	0	x $ 18.00		$	0.00
Independent claims	1	- 3 (at least 3) =	0	x $ 78.00		$	0.00
If any proper multiple dependent claims now added for first time, add $260.00 (ignore improper)						$	0.00
					SUBTOTAL	$	**760.00**
If "small entity," then enter half (1/2) of subtotal and subtract						-$(	380.00)
					SECOND SUBTOTAL	$	**380.00**
Assignment Recording Fee ($40.00)						$	0.00
					TOTAL FEE ENCLOSED	$	**380.00**

Any future submission requiring an extension of time is hereby stated to include a petition for such time extension. The Commissioner is hereby authorized to charge any deficiency in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our **Account No. 14-1140.** A duplicate copy of this sheet is attached.

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NIXON & VANDERHYE P.C.
By Atty: Mary J. Wilson, Reg. No. 32,955

Signature: Mary J. Wilson

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

FERGUSON, Mark W.J. Atty. Ref.: 39-196

Div. of Serial No. 08/029,098 (Filed: May 13, 1998) Group Art Unit:

Filed: December 14, 1999 Examiner:

For: **PHARMACEUTICAL COMPOSITION CONTAINING INHIBITORS OF INTERFERON-GAMMA**

* * * * *

December 14, 1999

PRELIMINARY AMENDMENT

Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

Sir:

Kindly preliminarily amend this application prior to calculation of the fees.

IN THE CLAIMS:

Cancel claims 1-24 without prejudice.

Add the following new claims.

--25. A method for promoting the healing of chronic wounds comprising the use of a stimulator of IFN-γ.

26. A method according to claim 25, comprising administering to a site of wounding a stimulator of IFN-γ.

27. A method according to claim 25, comprising the use of between 7,500 and 15,000 IU IFN-γ.

28. A method according to claim 25, comprising stimulating IFN-γ either immediately prior to wounding or immediately after wounding.

29. The method according to claim 25 wherein the stimulator is selected from any one of the group IFN-γ or a partially modified form thereof, and an inhibitor of IFN-γ metabolism.

30. The method according to claim 25 wherein the stimulator is used in conjunction with a pharmaceutically acceptable carrier, diluent or excipient.

31. A method according to claim 25 used in conjunction with a method for promoting the healing of wounds or fibrotic disorders with reduced scarring.

32. A method according to claim 25 used in conjunction with a method for promoting the healing of chronic wounds.--

Respectfully submitted,

NIXON & VANDERHYE, P.C.

By [signature]
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PHARMACEUTICAL COMPOSITION CONTAINING INHIBITORS OF INTERFERON- GAMMA

The present invention concerns pharmaceutical preparations for promoting the healing of wounds or fibrotic disorders, in particular for promoting the healing of wounds or fibrotic disorders with reduced scarring, and for promoting the healing of chronic wounds.

By "wounds or fibrotic disorders" is meant any condition which may result in the formation of scar tissue. In particular, this includes the healing of skin wounds, the repair of tendon damage, the healing of crush injuries, the healing of central nervous system (CNS) injuries, conditions which result in the formation of scar tissue in the CNS, scar tissue formation resulting from strokes, and tissue adhesion, for example, as a result of injury or surgery (this may apply to e.g. tendon healing and abdominal strictures and adhesions). Examples of fibrotic disorders include pulmonary fibrosis, glomerulonephritis, cirrhosis of the liver, and proliferative vitreoretinopathy.

In particular, there is a lack of compositions for promoting the healing of wounds or fibrotic disorders with reduced scarring. Scar tissue formation, although providing mechanical strength to a healed wound, can be unsightly and may impair the function of the tissue.

This is particularly the case in wounds which result in scar tissue formation in the CNS, the scar tissue inhibiting the reconnection of severed or re-growing nerve ends, so significantly affecting their function.

There is also a lack of compositions for use in the treatment of chronic wounds, for example venous ulcers, diabetic ulcers and bed sores (decubitus ulcers), especially in the elderly and wheel chair bound patients. Such compositions may be extremely useful in patients where wound healing is either slow or in whom the wound

healing process has not yet started. Such compositions may be used to "kick-start" wound healing and may then be used in combination with compositions (e.g. those of PCT/GB93/00586) which promote the healing of wounds or fibrotic disorders with reduced scarring. Hence not only may a chronic wound be healed, but it may be healed with reduced scarring.

According to the present invention there is provided an inhibitor of IFN-γ (Interferon-γ) for use in promoting the healing of wounds and fibrotic disorders with reduced scarring.

IFN-γ (Type II or immune interferon) is produced primarily by T lymphocytes upon mitogen or antigen stimulation (Trinchieri *et al.*, 1985, Immunology Today, 6: 131). IFN-γ (both murine and human) exert their effects through specific, saturable, binding to a single class of high affinity receptors found on a variety of cells including fibroblasts, endothelial cells and monocytes/macrophages.

IFN-γ has been widely studied (see, for example, Kovacs, E.J., 1991, Immunology Today, 12(1): 17-23 - who states that IFN-γ decreases fibroblast proliferation and connective tissue production, i.e. inhibits scar tissue formation). Past studies of the effects of IFN-γ at wound sites have shown (Pittel, B. *et al.*, 1994, Plastic and Reconstructive Surgery, 93: 1224-1235) that in studies on the effect of intralesional injection of IFN-γ to hypertrophic scars (an abnormal thickening of muscle), most (6/7) patients showed relief of symptoms, and all patients showed reduced lesion size during treatment, although there was no change in the total collagen content. Duncan *et al* (1985, J. Exp. Med., 162: 516-527) and Amento *et al* (1985, J. Clin. Invest., 76: 836-848) have shown that IFN-γ inhibits collagen types I and III and fibronectin synthesis by dermal and synovial fibroblasts and collagen type II by chondrocytes in a dose-dependent manner. Murray *et al* (1985, J. Immunol., 134: 1619-1622) have also shown that IFN-γ is involved in macrophage activation *in vivo*. Tamai *et al* (1995, J. Invest. Dermatol.,

104: 384-390) have shown that IFN-γ is involved in the regulation of metalloproteases (MMP) and tissue inhibitor of metalloproteases (TIMP) in *in vitro* cell culture. Various uses for IFN-γ and antagonists of same are proposed in EP 0304291, EP 0528469, WO 92/06115, WO 91/02005, WO 88/07869, EP 0328255, WO 92/14480, WO 87/07842, WO 94/07497, and Lorat-Jacobs, H. *et al.*, 1994, Path. Res. Pract. 190: 920-922.

It appears that IFN-γ is a multi-potent molecule with many actions depending on the conditions of the environment to which it is added. Several groups have reported decreased collagen synthesis *in vitro* on addition of IFN-γ to cultures, and Granstein *et al* (1989, J. Invest. Dermatol., 93: 18-27) have shown inhibition of collagen deposition and hence healing with reduced scarring in wounds treated with IFN-γ. From these results, it appears that the treatment of sites (of wounds or fibrotic disorders) with IFN-γ would result in healing with reduced scarring.

Experiments undertaken (see 'Experimental' section below) have shown that, very surprisingly, the inhibition of IFN-γ actually promotes healing with reduced scarring, despite the teachings of the prior art.

The inhibitor may, for example, be a neutralising antibody. It may be a monoclonal antibody, a polyclonal antibody, a phage-derived antibody, a genetically engineered antibody (e.g. diabody), or antibody derived from a transgenic mouse.

Alternatively, the inhibitor may be anything which inhibits IFN-γ from interacting with its receptor (i.e. antagonises IFN-γ receptor activation) or which inhibits the receptor's activation. It may, for example, be a molecule which mimics the IFN-γ receptor binding sequence and which binds to the receptor but does not activate it, thereby competitively inhibiting the binding of IFN-γ to the receptor and inhibiting the activation of the receptor.

The inhibitor may be used in conjunction with a pharmaceutically acceptable carrier, diluent or excipient.

The inhibitor may be used in conjunction with a composition for promoting the healing of wounds or fibrotic disorders with reduced scarring.

The inhibitor may be used in conjunction with a composition for promoting the healing of chronic wounds.

Also provided according to the present invention is a method for promoting the healing of wounds or fibrotic disorders with reduced scarring comprising inhibiting IFN-γ.

The inhibition may be achieved by administering to a site an inhibitor of IFN-γ. By "site" is meant a site of wounding or fibrotic disorder. The inhibitor may be an inhibitor according to the present invention.

Between about 300 and about 30,000 IU IFN-γ may be inhibited.

The IFN-γ may be inhibited immediately prior to wounding/onset (by "onset" is meant the onset of a fibrotic disorder). It may be inhibited immediately after wounding/onset, although it may also be inhibited later, for example within approximately 3 or 7 days of wounding/onset.

The method may be used in conjunction with a method for promoting the healing of wounds or fibrotic disorders with reduced scarring.

The method may be used in conjunction with a method for promoting the healing of chronic wounds.

According to a further aspect of the present invention there is also provided a stimulator of IFN-γ for use in promoting the healing of chronic wounds. .

The experiments (see 'Experimental' section below) have also shown that, very surprisingly, treatment of a site with IFN-γ actually promotes the deposition of collagen and healing with increased scarring and therefore may be used to promote the healing of chronic wounds.

By "stimulator" is meant anything which may stimulate (i.e. agonise) the quantity or efficacy of active IFN-γ at a site or the activation of the IFN-γ receptor. This may be IFN-γ itself or partially modified form of IFN-γ. A partially modified form of IFN-γ may, for example, have a longer half-life than IFN-γ. Alternatively, it may be an inhibitor of IFN-γ metabolism.

Partial modification may be by way of addition, deletion or substitution of amino acid residues. A substitution may for example be a conserved substitution. Hence a partially modified molecule be a homologue of the molecule from which it was derived. It may have at least 40%, for example 50, 60, 70, 80, 90 or 95%, homology with the molecule from which it is derived.

The stimulator may be used in conjunction with a pharmaceutically acceptable carrier, diluent or excipient.

The stimulator may be used in conjunction with a composition for promoting the healing of wounds or fibrotic disorders with reduced scarring.

The stimulator may be used in conjunction with a composition for promoting the healing of chronic wounds.

Also provided according to the present invention is a method for promoting the healing of chronic wounds comprising stimulating IFN-γ at a site. By "stimulating"

is meant increasing the quantity or efficacy of active IFN-γ at a site or the activation of the IFN-γ receptor.

The stimulation may be achieved by administering to a site a stimulator of IFN-γ. The stimulator may be a stimulator according to the present invention.

Between about 7,500 and 15,000 IU IFN-γ may be administered to stimulate a site.

The IFN-γ may be stimulated immediately prior to wounding. It may be stimulated immediately after wounding, although it may also be stimulated later, for example within approximately 3 or 7 days or longer of wounding.

The method may be used in conjunction with a method for promoting the healing of wounds or fibrotic disorders with reduced scarring.

The method may be used in conjunction with a method for promoting the healing of chronic wounds.

The invention will be further apparent from the following example which shows, by way of example only, forms of inhibition of IFN-γ and promotion of healing with reduced scarring, and of promotion of healing of chronic wounds.

EXPERIMENTAL

Method

84 male CD1 mice, 12 to 15 weeks old (Charles River) were anaesthetised using equal parts halothane, oxygen and nitrous oxide. 2 x 1cm full-thickness incisions (through the panniculus carnosus) were made 3cm from the base of the skull and 1cm either side of the dorsal midline.

Test solutions used were anti-IFN-γ, IFN-γ and PBS. Anti-IFN-γ comprised monoclonal antibody against murine IFN-γ (MuIFN-γ; = rat IgG'2a). Antibodies were obtained as ascites fluid from thymusless nude-mice innoculated with the F3 hybridoma clone (J. Immunol., 1987, 138: 4178) and purified by affinity chromatography on an anti-rat kappa-chain mAb. The neutralisation potential of the antibody was 1/1,000,000 against 30U/ml of MuIFN-γ and contained 1.25 ng/ml endotoxin. IFN-γ was Chinese hamster ovary (CHO) cell-derived reconbinant MuIFN-γ purified by affinity chromatography on anti-IFN-γ mAb. The IFN-γ was at an initial concentration of 300,000 IU/ml (endotoxin: 73pg/ml).

Animals were split into several groups as follows:

Group A: Animals were treated with a single intraperitonal (IP) injection (100µl) of neat anti-IFN-γ antibodies prior to wounding.

Group B: Animals were treated with a single intradermal (ID) injection of 50µl or 25µl of anti-IFN-γ antibodies (diluted with PBS) prior to wounding.

Group C: Animals were treated with a single ID injection of IFN-γ (15,000 or 7,500 IU) prior to wounding.

Group D: Animals were treated with ID injections of IFN-γ (15,000 or 7,500 IU) on day 0 prior to wounding and days 3 and 7 post-wounding.

Group E: Animals were treated with a single control IP injection of PBS (phosphate buffered saline) on day 0 prior to wounding (control).

Group F: Animals were treated with a single control ID injection of PBS on day 0 prior to wounding.

Group G: Animals were treated with an ID injection of PBS on day 0 prior to wounding and days 3 and 7 post-wounding.

Animals were killed by chloroform overdose on days 7, 14, 70 & 120 post-wounding. Wounds were excised and bisected for routine histology and immunocytochemistry. 7μm wax sections were cut and stained for Haemotoxylin and Eosin to assess cell invasion and re-epithelialisation, and for Masson's Trichome to assess collagen deposition and orientation.

Results

Anti-IFN-γ antibodies:

No difference was observed between control wounds and treated wounds at any time point in the animals treated with a single IP injection.

With a single ID injection of anti-IFN-γ, there were no differences compared to controls at 7 and 14 days. However. by 70 and 120 days, marked differences in the orientation of the collagen fibres within the treated wound were observed.

Anti-IFN-γ treatment is anti-scarring, improving the quality of dermal architecture, despite the prior art observations. While the fibres were still relatively small and compacted immediately under the epidermis, they are randomly orientated, whereas in the mid and deep dermis the collagen fibres were less compacted and were orientated in a "basketweave" fashion. Control wounds (scarred) had compacted parallel collagen fibres throughout the wound area.

IFN-γ

At the early time points (7 and 14 days), all the IFN-γ-treated wounds (in both injection regimes) showed increased inflammation and angiogenesis in a dose-dependent manner, i.e. lower doses, although worse than control wounds, were not as bad as wounds treated with higher doses of IFN-γ.

By 70 and 120 days, the wounds treated on days 0, 3 and 7 post-wounding with a high dose of IFN-γ showed marked fibrosis (i.e. scarring). Macroscopically, the wounds were raised and, microscopically, densely packed collagen in large swirling bundles within the wound margins was observed. These treated wounds also showed residual inflammation at the base of the wound, compared to control wounds. Again, this scarring was dose-dependent, i.e. the greater the dose of IFN-γ, the greater the scarring.

Discussion

Previous work has shown that administration of IFN-γ to wounds inhibits collagen synthesis, suggesting that it may be useful as an anti-scarring agent. Other workers have shown that treatment of keloids or hypertrophic scars with IFN-γ decreases the size of the scar.

Contrary to these findings, these experiments have shown that, very surprisingly, the early treatment of wounds with IFN-γ causes fibrosis with raised scars that are packed full of collagen, whereas treatment of incisional wounds with antibodies to IFN-γ results in improved healing with collagen fibres orientated in a "basketweave" fashion resembling normal dermis (i.e. scarring is reduced).

AMENDED CLAIMS

[received by the International Bureau on 5 August 1997 (05.08.97);
original claims 1-24 replaced by amended claims 1-24 (3 pages)]

1. The use of an inhibitor of IFN-γ in the manufacture of a medicament for promoting the healing of wounds or fibrotic disorders with reduced scarring.

2. The use of an inhibitor of IFN-γ according to claim 1, the inhibitor comprising a neutralising antibody.

3. The use of an inhibitor of IFN-γ according to either one of claims 1 or 2, the inhibitor being selected from any one of the group of a monoclonal antibody, a polyclonal antibody, a phage-derived antibody, a genetically engineered antibody and an antibody derived from a transgenic mouse.

4. The use of an inhibitor of IFN-γ according to any one of claims 1-3 wherein the inhibitor prevents IFN-γ interacting with its receptor.

5. The use of an inhibitor of IFN-γ according to any one of the preceding claims for use in conjunction with a pharmaceutically acceptable carrier, diluent or excipient.

6. The use of an inhibitor of IFN-γ according to any one of the preceding claims for use in conjunction with a composition for promoting the healing of wounds or fibrotic disorders with reduced scarring.

7. The use of an inhibitor of IFN-γ according to any one of the preceding claims for use in conjunction with a composition for promoting the healing of chronic wounds.

8. A method for promoting the healing of wounds or fibrotic disorders with reduced scarring comprising the use of an inhibitor of IFN-γ according to any one of the preceding claims.

9. A method according to claim 8, comprising administering to a site of wounding or fibrosis an inhibitor of IFN-γ.

10. A method according to any one of claims 8-9, comprising inhibiting between about 300 and about 30,000 IU IFN-γ.

11. A method according to any one of claims 8-10, IFN-γ being inhibited either immediately prior to wounding/onset or immediately after wounding/onset.

12. A method according to any one of claims 8-11 used in conjunction with a method for promoting the healing of wounds or fibrotic disorders with reduced scarring.

13. A method according to any one of claims 8-12 used in conjunction with a method for promoting the healing of chronic wounds.

14. The use of a stimulator of IFN-γ in the manufacture of a medicament for promoting the healing of chronic wounds.

15. The use of a stimulator of IFN-γ according to claim 15 wherein it is selected from any one of the group of IFN-γor a partially modified form thereof, and an inhibitor of IFN-γ metabolism.

16. The use of a stimulator of IFN-γ according to either one of claims 14 or 15 in conjunction with a pharmaceutically acceptable carrier, diluent or excipient.

17. The use of a stimulator of IFN-γ according to any one of claims 15-17 in conjunction with a composition for promoting the healing of wounds or fibrotic disorders with reduced scarring.

18. The use of a simulator of IFN-γ according to any one of claims 15-18 in conjunction with a composition for promoting the healing of chronic wounds.

19. A method for promoting the healing of chronic wounds comprising the use of a stimulator of IFN-γ according to any one of claims 14-18.

20. A method according to claim 19, comprising administering to a site of wounding a stimulator of IFN-γ.

21. A method according to either one of claims 19 or 20 comprising the use of between about 7,500 and 15,000 IU IFN-γ.

22. A method according to any one of claims 19-21, comprising stimulating IFN-γ either immediately prior to wounding or immediately after wounding.

23. A method according to any one of claims 19-22 used in conjunction with a method for promoting the healing of wounds or fibrotic disorders with reduced scarring.

24. A method according to any one of claims 19-23 used in conjunction with a method for promoting the healing of chronic wounds.

39-138
F3A/SDR/D088063PUS

Nixon & Vanderhye P.C. (12/95)

RULE 63 (37 C.F.R. 1.63)
DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PHARMACEUTICAL COMPOSITION CONTAINING INHIBITORS OF INTERFERON-GAMMA

the specification of which (**check** applicable **box(s)**):

☐ is attached hereto

☒ was filed on **February 18, 1998** as U.S. Application Serial No. **Unassigned** (Atty Dkt. No. **39-138**)

☒ was filed as PCT International application No. **PCT/GB96/01949** on **9 August 1996**

and (if applicable to U.S. or PCT application) was amended on **February 18, 1998**

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with 37 C.F.R. 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed or, if no priority is claimed, before the filing date of this application:

Priority Foreign Application(s):

Application Number	Country	Day/Month/Year Filed
9516967.8	Great Britain	18 August 1995

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

Application Number	Date/Month/Year Filed

I hereby claim the benefit under 35 U.S.C. 120/365 of all prior United States and PCT international applications listed above or below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior applications in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. 1.56 which occurred between the filing date of the prior applications and the national or PCT international filing date of this application.

Prior U.S./PCT Application(s):		Status: patented pending, abandoned
Application Serial No.	Day/Month/Year Filed	
PCT/GB96/01949	9 August 1996	abandoned

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon. And I hereby appoint **NIXON & VANDERHYE P.C., 1100 North Glebe Rd., 8th Floor, Arlington, VA 22201-4714, telephone number (703) 816-4000 (to whom all communications are to be directed)**, and the following attorneys thereof (of the same address) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent: Arthur R. Crawford, 25327; Larry S. Nixon, 25640; Robert A. Vanderhye, 27076; James T Hosmer, 30184; Robert W. Faris, 31352; Richard G. Besha, 22770; Mark E. Nusbaum, 32348; Michael J. Keenan, 32106; Bryan H. Davidson, 30251; Stanley C Spooner, 27393; Leonard C. Mitchard, 29009; Duane M. Byers, 33363; Jeffry H. Nelson, 30481; John R. Lastova, 33149; H. Warren Burnam, Jr 29366; Thomas E. Byrne, 32205; Mary J. Wilson, 32955; J. Scott Davidson, 33489; Alan M. Kagen, 36178; William J. Griffin, 31260; Robert A. Molan, 29834, B. J. Sadoff, 36663; James D. Berquist, 34776; Updeep S. Gill, 37334.*

1. Inventor's Signature: [signature] Date: 1st May 1998

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FOR ADDITIONAL INVENTORS, check box ☐ and attach sheet with same information and signature and date for each.

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